High Risk of Suicide in Behavioral Variant Frontotemporal Dementia

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ABSTRACT

Background: Recent studies reported an increased risk of suicidality in behavioral variant Frontotemporal Dementia (bvFTD). Aim of the study was to determine the prevalence of suicidal ideation and attempts in bvFTD patients, evaluating possible risk factors for suicidality.

Methods**:** Risk of suicide was assessed using the Scale for Suicide Ideation (SSI) in 35 bvFTD patients and 25 controls.

Results**:** According to SSI, 40% of bvFTD patients had suicidal ideation in comparison to 8% of controls (p=.009). Four bvFTD patients have attempted suicide versus none control (p=.006). BvFTD patients with suicide risk showed higher levels of anxiety, depression, stress and hopelessness than patients without suicide risk (p<.001). Patients who attempted suicide were younger, and had a longer disease duration than those with only suicide ideation. Intriguingly, 40% of patients with parkinsonism presented high level of suicide ideation.

Conclusions**:** Our findings show that bvFTD patients have a high risk of suicide. Additional studies in larger population are needed to confirm our results.

Key words: bvFTD, frontotemporal dementia, FTD, suicide, SSI, parkinsonism.

INTRODUCTION

The term Frontotemporal Dementia (FTD) encompasses a spectrum of neurodegenerative diseases clinically characterized by a progressive decline in both behavior and language, related to deposition of misfolded proteins in frontal and temporal lobes. Behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA) are the main clinical subtypes of FTD [1].

FTD is the second cause of presenile dementia, and bvFTD represents the most frequent subtype [2, 3]. This form is clinically characterized by prominent behavioral disturbances, including disinhibition, impulsivity, perseverations and loss of empathy, that are associated with deterioration of social conduct and impairment of cognition [1,4]. Recently, a complex and intriguing relationship between bvFTD and several psychiatric disorders has been described. Psychiatric symptoms may represent the first clinical signs of bvFTD, even several years before the onset of behavioral and cognitive symptoms [5].

In patients with overall dementia, the risk of suicide is generally considered low [6-8]. However, a growing body of research suggests that mood changes, severity of cognitive impairment, and awareness of disease, may lead patients with different forms of dementia to be more vulnerable to suicidal behavior [8-12]. To date, literature is scarce about the suicide risk in patients with bvFTD. In 2012, a first case report described a patient with bvFTD who committed suicide a few months after the diagnosis [13]. Subsequently, a retrospective study reported a higher risk of suicidal behavior in bvFTD patients when compared to controls [14]. At present, prevalence and risk factors for suicide have not been adequately investigated in bvFTD.

Thence, primary aim of our study was to determine the prevalence of both suicidal ideation and suicidal attempts in a cohort of patients with bvFTD, according to a case-control strategy. A secondary aim was to evaluate the possible neuropsychological and neuropsychiatric risk factors correlated with suicidality.

METHODS

Participants

Thirty-five patients with a diagnosis of probable bvFTD (18 men, 17 women; mean age± SD: 70.1± 6.3 years) attending the Aging Brain and Memory Clinic of the Department of Neuroscience "Rita Levi Montalcini", University of Torino, Italy, were recruited for the study. The diagnosis of bvFTD was performed according to Rascovsky et al. criteria [15].

Patients underwent extensive clinical, neuropsychological, and neuroimaging investigations (brain MRI and 18-FDG PET). The clinical diagnosis was supported by CSF biomarkers (beta amyloid, total tau, and phosphorylated tau), in order to exclude Alzheimer's disease pathology. Patients were screened for genetic variants in the major FTD-related genes (*MAPT*, *GRN*, and *C9orf72*) [19]. A group of 25 healthy age- and education-matched subjects (8 men, 17 women; mean age ± SD: 68.1±7.4 years) served as controls. Patients were excluded from the study if they had (a) an Ano-sognosia Questionnaire-Dementia (AQ-D) [16] score ≥ 32, (b) a Mini Mental State Examination (MMSE) [17] score < 24, and (c) a Token Test (TT) [18] score < 26.5.

Written informed consent was obtained from all participants and the study was approved by the Hospital Ethics Committee.

Assessment of suicidality

Suicide risk was measured using the Scale for Suicide Ideations (SSI) [20], as suggested by the Italian Society of Psychiatry [www.psichiatrica.it]. SSI is a 19-item semistructured interview performed by a clinician, based on patient's answers, evaluating self-destructive and suicide thoughts within the last week period. In addition, data on previous suicide attempts are collected by the test. In details, SSI consists of five screening domains: three items exploring the wish to live or die, and two items evaluating the desire to attempt suicide. Each item consists of a 3-point scale, ranging from 0 to 2, to quantify suicidal intensity. Fourteen additional questions are administered if the subjects report any active or passive thoughts to commit suicide. Answers include duration and frequency of ideation, sense of control over making an attempt, number of deterrents, and amount of actual preparation for a contemplated attempt. The overall score ranges from 0 to 38 and, according to literature, a score ≥ 6 has been used as threshold for suicidal ideation [21,22]. Suicide attempt refers to potentially self-injurious behavior thought and performed with the purpose to kill oneself.

Neuropsychological Assessment

Global cognitive impairment was assessed through Mini Mental State Examination (MMSE) [17], Clinical Dementia Rating Scale (CDR) [23], and Frontal Assessment Battery (FAB) [24]. Other cognitive domains were also investigated: attention and executive functions with Trail Making Test (TMT) [25,26], verbal learning and memory with Rey 15 Words Auditory Learning Test (RAVLT) [27] and language comprehension with TT [18,25]. In addition, Reading the Mind in the Eyes Test (RMET) has been used to evaluate the ability to recognize the mental state of others using the expressions of the eyes [28,29]. Patients' awareness of disease was assessed using the AQ-D scale [16]. Finally, autonomy in daily living was estimated with both Activities of Daily Living (ADL) [30] and the Instrumental Activities of Daily Living Scale (IADL) [31].

Neuropsychiatric Assessment

Each group underwent specific questionnaires on behavioral and mood changes. Apathy was assessed with Apathy Evaluation Scale-Clinician Version (AES-C) [32], depression was examined with Hamilton Depression Rating Scale (HDR-S) [33], anxiety and stress were evaluated with Hamilton Anxiety Rating Scale (HAR-S) [34] and Perceived Stress Scale (PSS) [35]. Finally, Barratt Impulsiveness Scale (BIS-11) [36] and Beck's Hopelessness Scale (BHS) [37] were also used to evaluate patient's impulsiveness and hopelessness.

Statistical Analysis

All data were analyzed using SPSS Version 21.0 for Windows (IBM SPSS Statistics, Inc, Chicago, IL, USA). Demographic and clinical variables were compared using T-test and $\chi 2$. Neuropsychological and neuropsychiatric characteristics were analyzed using T-test and multivariate analysis of variance. Pearson's rho with Bonferroni correction was used to evaluate the correlation between suicidal ideation and performance on the neuropsychological and neuropsychiatric tests. The significance level was set at $p<.05$ for all analyses, and $p<.01$ for Bonferroni correction.

RESULTS

Assessment of suicidality

Demographic and clinical characteristics of patients and controls are summarized in table 1. According to SSI scale, 40% of bvFTD patients showed suicide ideation, in comparison with 8.0% of controls ($p= .009$). Subsequently, according to the obtained scores, all the subjects involved in the study were divided into two different groups: A. subjects with risk of suicide (SR), and B. subjects without risk of suicide (NS).

When looking at overall bvFTD group, fourteen bvFTD patients had a risk of suicide (bvFTD-SR), and twenty-one bvFTD patients showed no suicide risk (bvFTD-NS). In the subgroup of bvFTD at risk of suicide, 10 patients showed a suicide ideation alone (71.4%), whereas four patients in addition to suicidal ideation, also had attempted suicide (28.6%). In details, three patients with bvFTD had attempted suicide with a non-fatal self-poisoning, while one bvFTD patient tried to defenestrate himself. When bvFTD patients attempted suicide, they were not taking any L-dopa or dopaminergic treatments. In control group, according to the SSI, two controls (8%) had a risk of suicide (Cont-SR), whereas the remaining subjects showed no suicide risk (Cont-NS).

BvFTD patients who attempted suicide showed a higher global SSI score in comparison with those who presented suicidal ideation alone ($p < .001$). No differences were found in global SSI scores between males and females patients with bvFTD at risk of suicide.

Neuropsychological Assessment

The overall group of bvFTD patients showed higher levels of functional and cognitive impairment ($p<.005$) and were more apathetic and impulsive ($p<.001$) when compared with controls, as expected. Interestingly, in the bvFTD group, no differences in the neuropsychological characteristics were found when comparing bvFTD patients at suicide risk and bvFTD patients with no suicide risk (Table 2).

Neuropsychiatric Assessment

Using multivariate analysis for the neuropsychiatric data, patients with bvFTD presented higher levels of apathy, impulsivity and hopelessness ($p < .001$) when compared with controls. In the bvFTD group, patients at suicide risk showed higher scores in depression, anxiety, stress, and hopelessness ($p<.001$) in comparison with bvFTD patients with no suicide risk (Fig. 1).

Clinical characteristics

Evaluating the clinical characteristics of bvFTD patients, we observed that the subjects who attempted suicide were younger ($p<.05$), and had a longer duration of the disease ($p=.007$) than bvFTD patients with only suicide ideation. In addition, gender and education did not influence the suicide risk in bvFTD.

In the overall bvFTD group, seven out of 35 patients showed parkinsonism, mainly presenting with bradykinesia and axial rigidity. Notably, bvFTD patients with extrapyramidal signs had higher level of suicide ideation (OR= 15; 95% CI: 1.55-145.23, $p=.019$) than remaining patients.

In this dataset of patients with bvFTD, one subject carried a missense mutation in *GRN* gene and one an expansion in *C9orf72* gene. However, we do not detect any clear link between suicide risk and mutations in known FTD-related genes due to the paucity of patients with mutations.

DISCUSSION

To the best of our knowledge, this is the first study evaluating both the suicidal behavior and the suicidal ideation in patients with behavioral variant frontotemporal dementia. Our findings showed that patients with bvFTD are at higher risk of suicide, since approximately 40% of our patients showed a suicidal ideation, and more than 10% attempted suicide.

Worldwide, suicidal behavior is a major cause of disability and the fifteenth cause of death according to WHO reports [38]. Globally, the lifetime prevalence of suicidal ideation is 9.2%, and of suicidal attempts is 2.7% [39]. Therefore, investigating the prevalence of suicidal behavior as well as its neurobiological bases in patients with major neurocognitive disorders is paramount. The

risk of committing suicide in dementia is generally low, and suicide attempts are present in less than 1% of patients [40,41]. However, a recent study investigating the suicidal behavior in patients with FTD showed a higher risk of attempt of suicide in respect to controls [14]. In our study, we confirmed these results in patients with bvFTD, the main subgroup of FTD, and we further showed that, not only the suicidal behavior, but also the suicidal ideation is high in these patients. It is of interest to note that, in our bvFTD population, the frequency of suicide behavior overlaps the one observed in Huntington's disease, a neurodegenerative disease known to be associated with high risk of suicide [42,43]. Therefore, additional clinical and epidemiological studies are warranted in order to better investigate the risk of suicide in different neurodegenerative disorders.

In our study, bvFTD patients who have attempted suicide were younger and showed a longer duration of the disease than patients with only suicide ideation. Our findings are supported by a growing body of researches on suicidality in patients with dementia, reporting that young age is a risk factor for suicide behavior [9,11]. Intriguingly, no association between gender and risk of suicide was found in our patients. This finding is in line with other research focused on suicide behavior in patients with neurodegenerative disorders, that not confirmed a higher tendency of suicidality in females [44]. Recently, a case-control study on neurological disorders and suicide attempts showed that males with neurological diseases had a higher risk of attempting suicide than female patients [45]. Therefore, further studies assessing the risk of suicide in patients with chronic neurological disorders according to gender are needed.

Psychological aspects as anxiety and depression related to the diagnosis of a neurodegenerative disorder at an earlier age could drive suicidal behavior [11,12]. In our patients, risk factors for suicide include depression, anxiety, stress, and hopelessness. Since no therapies for the disease are currently available, bvFTD patients may experience an elevated stress and a sense of hopelessness for their future, leading to suicidal ideations.

Neurobiological bases of suicidal behavior have been investigated only in recent years. Some studies suggested a role for the prefrontal regions in suicide [46]. Post-mortem studies reported a reduction of presynaptic serotonin transporter sites in the prefrontal cortex, including the inferior frontal gyrus and the orbitofrontal cortex [47], brain areas typically involved in the pathogenesis of bvFTD. In addition, an increased in 5-HT1A binding was found in these regions, suggesting that the serotonergic dysfunction in suicide victims might be due to gene expression changes in dorsal and ventral regions of the prefrontal cortex [47]. Finally, reduced concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid are associated with suicidal behavior in patients with depressive disorders and schizophrenia [48]. All these findings support the role of the serotoninergic system in the pathogenesis of suicide behavior.

In our study, approximately 20% of the overall patients presented extrapyramidal signs, that is consistent with previously reported on the prevalence of parkinsonism in bvFTD 4. Intriguingly, we observed that 40% of bvFTD patients with extrapyramidal signs showed higher level of suicide ideation than patients without parkinsonism. A recent case report described a suicide attempt in a patient with bvFTD with parkinsonian symptoms [13]. These clinical findings could be of importance for clinicians treating these patients. This could also suggest an involvement of subcortical regions and basal ganglia in the risk of suicide. In literature, suicidal ideations have been reported to occur in approximately in 23% of patients with Parkinson's disease [49]. In addition, there are some evidences in depressed suicide victims for a reduced dopamine turnover in the nucleus accumbens, caudate, and putamen [50]. Furthermore, gene polymorphisms of the dopaminergic system have been reported to be involved in the biological susceptibility to suicide [51]. Finally, a recent study showed that a haplotype in the dopamine receptor *DRD2* gene is involved in suicidal behaviour in alcohol dependent subjects [52]. Further investigations on the genetic susceptibility of suicide are therefore suggested in bvFTD patients.

Finally, we suggest that suicide risk should be considered when evaluating patients with bvFTD, in particular in young age. Suicide ideation and attempts are strongly predictive of suicide deaths, but the risk of suicide in patients with dementias other than Alzheimer's disease has often been underestimated. Therefore, this study can have several potential clinical implications. First, a better understanding of risk factors associated with suicidal behavior in patients with bvFTD can increase the use of routine suicide evaluations. Secondly, an early identification of subjects who have suicidal ideation can help the clinicians to suggest psychological supports and to prescribe more effective individualized pharmacological therapies. In schizophrenia, there are some evidences that the typical antipsychotic drugs, associated or not with antidepressants, as well as the atypical neuroleptic drugs as clozapine, have an effect on suicidal behavior and reduce the risk of suicide [53]. This therapeutic approach could also be applied to patients with bvFTD.

Our study has some limitations that deserve to be mentioned. First, the study population is relatively small; however, the subjects recruited for the study have been extensively investigated in order to exclude any other forms of dementia. Secondly, our work involves only bvFTD and does not capture the language forms of FTD. Previously, in patients with semantic dementia has been reported that the risk of committing suicide is particularly high along with an accompanying awareness of their cognitive impairment [14]. Contrariwise, a previous retrospective study on frontotemporal lobar degeneration reported that all the patients with suicidal behavior had the behavioral variant of FTD [14]. Third, our control population is unbalanced in term of gender. Notwithstanding, in our controls the prevalence of suicide ideation overlaps that reported in WHO findings [38]. Fourth, in our study bvFTD patients present a lower level of education in respect to controls. However, in Italian population, the attainment of high level of education is associated with a greater risk of suicide, thence the lower level of schooling in bvFTD may not have influenced the suicide ideation [54]. Fifth in our study, suicide risk was assessed using the SSI as suggested by Italian psychiatric guidelines, and the

use of combined suicide scales might provide additional clinical data. Finally, the majority of the subjects involved in the study are aware of their disorder. In literature, it is unclear if a preserved insight potentially increases the risk of suicidal behavior in patients with neurodegenerative disorders.

In conclusion, our data showed that patients with bvFTD are at high risk for suicide. Additional studies are needed in order to further investigate the suicide risk in bvFTD, and to elucidate the underlying neurobiological and neurocognitive mechanisms.

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TABLE 1. Demographic characteristics of patients with bvFTD and controls.

	bvFTD	**Controls**
Gender (M/F)	18/17	8/17
Age (yrs; mean ± SD)	70.14 ± 6.32	68.12 ± 7.44
Education		
8 yrs	62.86% (22)	32.00% (8)
13 yrs	25.71% (9)	40.00% (10)
>13 yrs	11.43% (4)	28.00% (7)
Onset of disease (yrs)	65.00 ± 7.82	-
Duration of disease (yrs)	4.08 ± 3.27	-

Abbreviations: M= male; F= female

TABLE 2. Neuropsychological, Neuropsychiatric and Functional assessment synopsis of patients with bvFTD, according to the presence of the suicide risk.

	bvFTD-SR	bvFTD-NS	p value
MMSE	24.1 ± 3.4	23.7 ± 2.8	.685
CDR	1.0 ± 0.7	1.1 ± 0.5	.858
FAB	10.7 ± 3.6	10.9 ± 3.2	.881
TMT-A	121.9 ± 124.1	103.4 ± 76.9	.755
TMT-B	312.7 ± 137.9	290.8 ± 174.1	.706
TMT B-A	232.2 ± 130.9	201.3 ± 149.8	.624
RAVLT	21.3 ± 7.7	22.3 ± 6.7	.725
TT	33.0 ± 2.4	32.1 ± 2.6	.579
RMET	16.6 ± 4.1	18.0 ± 5.7	.349
AES-C	13.9±12.3	23.7±18.7	.940
HDR-S	26.4±9.0	11.5±5.5	.000*
HAR-S	24.6±7.5	10.1±5.7	.000*
PSS	27.6±3.2	16.1±5.2	.000*
BIS-11	78.4±8.1	73.1±13.0	.188
BHS	15.5±4.7	8.6±5.1	.000*
AQ-D	-2.5 ± 10.4	4.3 ± 9.0	.075
ADL	4.8 ± 1.5	5.7 ± 5.0	.070
IADL	5.2 ± 2.4	5.0 ± 2.2	.754

Abbreviations: bvFTD-SR = bvFTD patients with risk of suicide; bvFTD-NS = bvFTD without risk of suicide; MMSE= Mini-Mental State Examination; CDR= Clinical Dementia Rating Scale; FAB= Frontal Assessment Battery; TMT= Trial Making Test; RAVLT= Rey 15 Words Auditory Learning Test,; TT= Token Test; RMET = Reading the Mind in the Eyes test; AES-C= Apathy Evaluation Scale-Clinician Version; HDR-S= Hamilton Depression Rating Scale; HAR-S= Hamilton Anxiety Rating Scale; PSS= Perceived Stress Scale; BIS-11= Barratt Impulsiveness Scale; BHS= Beck's Hopelessness Scale; AQ-D= Awareness Questionnaire Disease, ADL= Activity of Daily Living Scale; IADL= Instrumental Activity of Daily Living Scale. All data are presented as mean ± SD.

Figure 1. Levels of hopelessness, impulsivity, depression, apathy, anxiety, and stress in patients with bvFTD. Data are presented as means ± SD of subjects' scores in questionnaires on behavioral and mood changes, according to the presence of suicide risk. bvFTD patients with risk of suicide (bvFTD-SR) show higher levels of hopelessness, depression, anxiety, and stress than bvFTD without risk of suicide (bvFTD-NS). * $p < .01$.

Abbreviations: BHS= Beck's Hopelessness Scale; BIS-11= Barratt Impulsiveness Scale; HDR-S= Hamilton Depression Rating Scale; AES-C= Apathy Evaluation Scale-Clinician Version; HAR-S= Hamilton Anxiety Rating Scale; PSS= Perceived Stress Scale.